REMARKS

Claims 68, 70-72, 75-80, 82-83, 85-96, 108-109, 111, and 115-126 are presently pending and under examination in the case. No amendments to the claims are made at this time.

As a preliminary matter, Applicant thanks the Examiner and her Supervisor for their time and courtesy during the telephonic interview on August 27, 2009. No agreements were reached. If the Examiner has any further questions in relation to the instant application or response, the Examiner is encouraged to contact the Agent for Applicant listed below.

During the interview, the difference between active pharmaceutical ingredient (API) size and granule size were discussed. Applicant notes that the claims are drawn to "a quick release pharmaceutical composition for oral administration". Therefore, the composition must have **both** the dissolution properties claimed and be prepared in a form that it can be portioned appropriately into uniform quantities for dosage, either in tablet or granule form, as would be required for a pharmaceutical composition. If the Examiner does not consider the preamble to provide a structural limitation to the claims, the teachings of the cited references as a whole must be considered. All of the references, other than Melia, are directed to pharmaceutical compositions that can be made into tablets. Modification of the teaching of the references such that the material could not be formed into a tablet would be contrary to the teachings of the cited art. Therefore, one must be able to consistently measure a specific quantity of the pharmaceutical composition, and optionally form the composition into a tablet.

Applicant provides herewith two references for consideration in conjunction with the arguments below.

1. Lieberman et al., *Pharmaceutical Dosage Forms*, Marcel Dekker, Inc. c. 1990, Second Edition, volume 2, pages 33-34.

2. J. Faith. Sneeze-free preparation of Luria Bertani (LB) broth. Available at http://wetlab.izzid.com/2007/Sept/Make_Luria_Bertani/.

Figure 21 on page 33 of Lieberman provides representations of the difference between API and granules. API is a pure substance, or a mixture of pure substances, that are not held together by a binding material. Physical properties of APIs vary widely. An API does not typically have the appropriate physical properties to allow it to be formed into granules or tablets (e.g., flow, hardness).

A granule is a mixture of a pure substance, such as an API, in a binder. The combination of the API in the binder can be prepared to provide homogeneously sized particulate material that includes one or more pure substances, e.g., API, with the carrier/ binder material, that has appropriate physical properties to allow the granules to be formed into a tablet (e.g., flow, hardness).

The figure shows several different types of particles encountered in tablet granulation dry blending. The drawings on the left side of the figure schematically represent pure substances or mixtures of substances, for example, one or more APIs, wherein each particle is a single substance. Depending on the uniformity of the shape of the pure substance(s), etc., the particles may or may not stick together in the absence of a binder, and may form irregular aggregates due to electrostatic forces. Surface forces can easily, and transiently, be overcome by forcing the pure substance through a mesh. However, depending on the specific properties of the API, forcing the material through a mesh may increase electrostatic interactions, exacerbating the problem of irregular aggregate formation. As the aggregates formed by electrostatic forces would not provide homogeneous aggregates, the material would not likely flow well and be difficult to portion making it unsuitable for a pharmaceutical composition.

Also, depending on the size and density of the pure substances in a mixture, the components may or may not form a homogeneous mixture. Particles of various sizes can settle out or rise to the top of the mixture of powders of different sizes and densities. Even after mixing the pure substances, the process of tableting can result in separation of various components of the mixture based on size, shape, and/ or density.

As shown in the right hand side of the figure, the pure substance(s) can be mixed with a binder or compacted and milled. The material can then be processed and/

or passed through a mesh to provide an aggregate of pure substance(s) with a binder, e.g., a granule. As the granules are uniform, the various shapes, sizes, densities, electrostatic forces, etc. of each of the individual pure substances no longer needs to be considered. Further, as the granules are larger than API, electrostatic and other surface interactions have far less effect on the granules. Therefore, after passage through an appropriately sized mesh (and drying when appropriate), the granules do not substantially form aggregates. The granules can be prepared in a size to reduce electrostatic interactions and increase uniformity, improving flow, allowing for consistent portioning of the material for preparation of a pharmaceutical composition as claimed.

These need to form API into a material that can be prepared into a dosage form is discussed in the text below the figure. Specifically the reference states:

> Large (sieve size range > 60 mesh) dry particles have a tendency to flow better than smaller dry particles, because they have greater mass. **Smaller particles (< 100 mesh) may create mixing problems because their surface areas are very great**… These forces may prevent the desired distribution of these smaller particles….
>
> As the particle size approaches 10 µm and below, weak polarizing electrical forces called van der Waals forces or cohesive forces also begin to affect the flow of the powder. **Both… forces usually inhibit powder flow**… [emphasis added]

Moreover, as discussed in the table on top of page 44 of Lieberman, as the particle size decreases relative to surface area, the effects of the surface forces are amplified, increasing problems with flow of materials having a particle size of 75 µM-200 µM. By increasing the mass of the particle to the surface area, the problems of surface forces are decreased. Particles having a size of < 100-75 µM have problems with flow due to both surface energy forces and static electrical forces.

Therefore, when making a composition for use as "a quick release pharmaceutical composition" including multiple components as claimed and taught in the cited references, **one must be concerned with homogeneous mixing and particle flow in addition to the dissolution properties**. If good particle flow cannot be achieved, appropriate dosage units cannot be prepared. If a homogeneous mixture cannot be formed, appropriate dosage units cannot be prepared.

Smaller particles are problematic both in providing the even distribution of the active ingredients and in the portioning of the mixture into dosage units. Rapid dissolution of a quick release pharmaceutical composition is desirable, but the dissolution properties of a particular particle of a therapeutic composition are only relevant if the composition can be prepared into a dosage unit. Portioning of an API into a dosage unit requires the generation of granules or other particles so that the API(s) can be mixed homogeneously and have good flow. This requires forming larger particles, not smaller particles. Based on these considerations, the suggestion that one of skill in the art would be motivated to use a smaller granule size based on the dissolution properties based on API size cannot stand. As all of the references cited, other than Melia, provide compositions to be formed into tablets, modification of the granules (e.g., by making them smaller) so that tablets can no longer be formed would make the references unsuitable for their desired purpose. Therefore, the references cannot be modified to provide granules of a size not useful for the preparation of a unit dosage form, particularly a tablet.

The second reference provided by Applicant was published after the filing date of the instant application, but addresses the comparison of the use of a powder material as compared to a granular material. The considerations regarding the advantages of the use of granular rather than powder material have not changed since the priority date of the instant application. Therefore, the reference can be properly considered.

During the telephonic interview, the question of does finer particulate material always dissolve more quickly than larger particulate material was discussed. Particularly, dissolution of sugar in water was discussed. Having not performed any experiments, it was agreed that based on our general experience, coarse sugar dissolves more slowly than superfine sugar in water. This suggests that a smaller granule size improves dissolution rate. However, a threshold can be crossed, for example in processing the sugar to a powder to provide confectionary sugar, wherein dissolution becomes slower with a smaller particle size. It is suggested, although not tested, that confectionary sugar would likely dissolve more slowly than superfine sugar

as it has an increased wetting time and has a tendency to clump (despite the inclusion of corn starch to reduce clumping).

Applicant notes that consistent measurement of granulated forms of sugar is more readily reproducible than with confectionary sugar. As used in this response, consistent measurement refers to the reproducibility of volume measurement to provide a reproducible weight of material. This consideration is relevant to the (automated) preparation of unit dosage forms where the volume of the material from which the dosage forms are to be made provides a specific weight reproducibly. Granulated sugar can easily be poured into a container (e.g., measuring cup), and a specific volume provides a relatively consistent weight of sugar. The same is not true for confectionary sugar for which a specific volume can vary largely in weight depending on the method of volume measurement.

It could be easily conceived that depending on the treatment of confectionary sugar prior to or during volumetric measurement that a volumetric measure of confectionary sugar would not provide a consistent weight of confectionary sugar. For example, if the confectionary sugar were poured directly from the bag, it would likely have clumps that would create gaps that would provide an inconsistent fill of the measuring cup (different weights per volume) upon repeated measurements. If pressure were used to compact the confectionary sugar, to obtain a full measure of confectionary sugar, the amount of pressure would determine the final weight of the sugar for the volume, again providing different weights for a single volume upon repeated measurements. (In considering dosage form preparation, filling, compacting, and filling again to obtain the desired tablet having a consistent dosage would not be practical.) If the confectionary sugar were sifted to make the particle size uniform shortly prior to measuring, one would likely be able to repeatedly obtain a more consistent weight per volume measure, however, it would again be different from the measurements made by the two other methods. Further, over time, or with manipulation of the confectionary sugar as would occur in tableting machines, the material would again form clumps resulting in inconsistencies in weight for a particular volume measure. Therefore, a finer powder does not always improve dissolution and

can make a material harder to use for the preparation of pharmaceutical compositions as claimed, and as required by all of the cited references other than Melia.

The Faith reference, provided by Applicant herewith, considers the same principles of dissolution rate and flow in relation to preparation of a common laboratory reagent, Luria Bertani (LB) broth. The concerns of the author are ease of preparation of the broth and reproducibility of preparation of the broth. Faith discusses two products, a premixed powdered LB, and a premixed granulated LB.

In relation to ease of use, Faith notes that the powdered LB generates a large amount of fine dust in the air during weighing which causes the author to sneeze or choke. In prior responses and herein, the problem of tableting fine powders using machines is addressed. The presence of excessive dust results in mechanical difficulties with the machines, choking the machines. As the instant claims and the cited references other than Melia are directed to a pharmaceutical composition, the ability to prepare a dosage form must be considered.

In relation to reproducibility, which is important with pharmaceutical compositions and culture media, Faith notes that the premixed powder clumps and is difficult to weigh. This is in contrast to the granules which "are easier to weigh and clump up less than a powder when mixed with water, so it is actually faster to prepare as well." In other words, the granular material has better flow making it easier to portion, and it does not form electrostatic aggregates in water making the dissolution faster. Therefore, based on Faith's teachings, a finer particulate material does not necessarily dissolve more rapidly than a larger particulate material.

In view of the discussion and the Faith reference provided, Applicant submits that one of skill in the art would not consider that a smaller particle size would always result in faster dissolution. Further, as the claims and all but one of the cited references are directed to a pharmaceutical composition, the ability to reproducibly prepare a dosage form must be considered. Applicant submits that one of skill in the art would not consider that the use of smaller particles for the preparation of a pharmaceutical

composition would be desirable or advantageous, or that a fine powder would invariably dissolve more quickly than a granule.

Examiner's Response to Applicant's Arguments and Rejection under 35 U.S.C. §103

The following rejections have been maintained in the Office Action.

Rejection of claims 68, 70-72, 75-80, 82-83, 85-86, 91-92, 95-96 and 108-111 under 35 U.S.C. 103(a) as being unpatentable over Nemoto et al. (JP 03-240729) in view of Bhardwaj et al. (US 5,578,316) and Melia et al. (Aliment. Pharmacol. Therap. (1989) 3, 513-525) .

Rejection of claims 87-90, 93-94 and 115-120 under 35 U.S.C. 103(a) as being unpatentable over Nemoto et al. (JP 03-240729) in view of Bhardwaj et al. (US 5,578,316), Melia et al. (Aliment. Pharmacol. Therap. (1989) 3, 513-525) and Penkler et al. (US 5,854,226).

Rejection of claims 121-122 under 35 U.S.C. 103(a) as being unpatentable over Nemoto et al. (JP 03-240729) in view of Bhardwaj et al. (US 5,578,316), Melia et al. (Aliment. Pharmacol. Therap. (1989) 3, 513-525) and Olinger et al. (US 5,651,988).

The rejections will be considered together.

All of the references cited, other than Melia, are related to the preparation of pharmaceutical compositions and dosage forms. Modification of the references to make the material no longer useful for preparation of a pharmaceutical composition and dosage forms would be contrary to the teachings of the references and therefore impermissible. That is, any suggestion to modify the references such that the material in the references is no longer appropriate for portioning in dosage forms and/ or formation into tablets makes the teachings of the references non-workable for their intended purpose. That is, reduction of granule size such that the material is no longer useful for the preparation of dosage forms would be contrary to the teachings of the references.

In the prior response to the Office Action, Applicant argued that API size, considered by Melia, is not relevant to granule size, which is what is taught by the other references combined with Melia. The instant Office Action states that

> Melia is used as a supporting reference that provides the relationship between reducing particle size, increasing dissolution rate and improving bioavailability. **Melia refers to the particle size of the API.** However, one of ordinary skill in the art would know that reducing the **particle size of granules of an API** would consequently lead to increasing dissolution rate because of the increased surface area of the reduced particle size API granules.

Applicant submits that an API granule would need to be large enough to have the necessary flow properties to allow the material to be prepared in unit dosage forms. Lieberman teaches that this size should preferably be at least about 200 µM. It is not possible to prepare a unit dosage form of an API granule of the size taught by Melia. API of the size taught by Melia could be formulated into granules with appropriate binders, but an API by itself is not typically a granule.

As shown in Lieberman, API size and granular size are distinct. Particle size of API is not altered by formulation of the particle into a granule. It is possible to have an API size such as that discussed by Melia present in a granule of substantially larger size. One cannot be motivated to modify granule size based on teachings regarding size of API. API needs to be prepared as granules to be prepared in a dosage form.

The instantly claimed invention, and all of the references cited in conjunction with Melia are directed to pharmaceutical compositions. To be a pharmaceutical composition, it is necessary that the material can be reproducibly prepared in a unit dosage form, typically by machine. In order to be prepared as a unit dosage form, the material must have desirable flow properties. **API sizes taught by Melia are 2.7 µM to 10 µM.** These size particles could not be directly prepared in unit dosage form (as demonstrated by Lieberman provided herewith an many references provided earlier in the prosecution of the instant application). Neither Meila nor the Examiner provides any demonstration that such small particles could be formed into tablets without first preparing the API as a granule, which Applicant suggests is how griseofulvin, the drug

discussed by Melia to provide motivation to reduce particle size, is prepared as a solid oral dosage form.

As griseofulvin exists commercially in a solid oral dosage form (product information of Grifulvin V® provided below) in combination with calcium stearate, colloidal silicon dioxide, starch, and wheat gluten, which can be used in the preparation of granules and subsequently tablet. Applicant submits that the API is likely formulated into granules which are subsequently formed into tablets to provide the solid oral dosage form.

> Grifulvin V®
>
> (griseofulvin tablets) Microsize and
>
> (griseofulvin oral suspension) Microsize Tablets/Suspension
>
> DRUG DESCRIPTION
>
> Griseofulvin is an antibiotic derived from a species of Penicillium. Each GRIFULVIN V Tablet contains either 250 mg or 500 mg of griseofulvin microsize, and also contains calcium stearate, colloidal silicon dioxide, starch, and wheat gluten. Additionally, the 250 mg tablet also contains dibasic calcium phosphate. Each 5 mL of GRIFULVIN V Suspension contains 125 mg of griseofulvin microsize and also contains alcohol 0.2%, docusate sodium, FD&C Red No. 40, FD&C Yellow No. 6, flavors, magnesium aluminum silicate, menthol, methylparaben, propylene glycol, propylparaben, saccharin sodium, simethicone emulsion, sodium alginate, sucrose, and purified water.

However, it is taught by Melia that the preferred dosage of griseofulvin is a 125 mg dose, which is provided as a liquid formulation which can provide no teachings or insight into the preparation of solid oral dosage forms.

The first paragraph of Melia clearly distinguishes the disintegration of the tablet (i.e., granule disintigration) from the dissolution of the drug (i.e., API), noting that drug dissolution is substantially a property of the drug. Specifically, Melia states:

> In the previous review we described how the **disintegration of a tablet or capsule** is a relatively rapid process and **it is controlled principally by the disintegrant within the dosage form**. In contrast, the **dissolution of the drug particles** is usually much slower and,

because it **is primarily an intrinsic property of the drug solid itself**, it is generally more difficult to control.

Therefore, Melia can be understood to teach that **selection of the disintegrant is a matter of choice which is not substantially relevant to dissolution rate of the API** which is a property intrinsic to the drug itself. Disintegrants expand and disaggregate when wet causing the tablet to break apart in the digestive tract, releasing the active ingredients for absorption. Disintegrant types generally include water uptake facilitators and tablet rupture promoters to ensure that the tablet is in contact with water and rapidly breaks down into smaller fragments, thereby facilitating dissolution of the API present in the tablet. Therefore, selection of a disintegrant with the desired porosity would provide the desired disintegration rate by the teachings of Melia. Fine particulate materials, such as API having a size of 10 µM or less, would not be expected to promote tablet rupture to ensure that the tablet is in contact with water.

The Office Action points to Bhardwaj to provide a link between granules and API granules. Specifically, the Office Action states that Bhardwaj teaches coating of "pure drug granular material" or "drug granules". However, Bhardwaj cannot teach drug particles of the size of Melia. **Bhardwaj teaches that particles must be of a particular size, specifically at least 180 µM** as "smaller particles present problems in the coating process." (col 2, lines 20-22). Therefore, if one wishes to coat particles, one must have particles at least 18 times larger than the largest particle size taught by Melia. Bhardwaj also notes problems of using particles that are too large. Bhardwaj demonstrates that depending on the formulation to be prepared, a number of factors must be taken into consideration **including manufacturing considerations**. Even if the API sizes taught by Melia could be granules, which they are not, the use of "pure drug granular material" of such a size is taught against. Particle size of at least 180 µM is required for preparation of the tablets of Bhardwaj. An API that cannot be prepared in a form that allows for preparation of appropriate unit dosage forms is of little use, as demonstrated by Bhardwaj, regardless of the properties of the API.

The Office Action states that the argument of Applicant that one of skill in the art would not recognize particle size to be a result effective variable is not persuasive based on

> the teachings of Melia (reducing particle size leads to increased dissolution rate and improved bioavailability), Klioze (rapidly disintegrating tablets with granules that are between 149µm and 840µm), and Bhardwaj (composition with granules between 200 and 400 microns) demonstrate that one of ordinary skill in the art would have recognized that particle size is **a result effective variable for increasing dissolution**. [emphasis added]

Applicant respectfully disagrees. To make a rejection for obviousness, a particular parameter must first be recognized as a result-effective variable, i.e., a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation. *In re Antonie*, 559 F.2d 618, 195 USPQ 6 (CCPA 1977) Although the cited references teach various size granules can be used, and that granule size may have an effect on manufacturing, granule size is not taught to be a results effective variable for dissolution.

Melia teaches that **reducing particle size of API** leads to increased dissolution rate and improved bioavailability. Particle size of API is not granule size of API, or API with disintegrant. As noted above, Melia teaches that granule size is a matter of choice that has little effect on drug dissolution rates.

Klioze teaches that "It has been found that granules ranging from about 20 to 100 mesh (U.S. Sieve series) are most advantageous in preparing the tablets of the invention." As the granule size is discussed in the manufacturing section of Klioze, **Applicant submits that Klioze teaches that granule size is a manufacturing consideration, not a consideration related to dissolution**, particularly as only one tablet was prepared and tested. Both portions A and B were granulated in the same manner. No comparisons were made. It is expected that all particles that were able to pass through a 30 mesh screen (of portion B) would subsequently pass through a 20 mesh screen, which has larger openings than a 30 mesh screen. Recycling of fines that passed through a 100 mesh screen removes the fine particulate matter, suggesting

that it is undesirable in the tablet (as discussed in *Remmington's* and noted below). Klioze cannot be understood to teach granule size as a results effective variable in regard to dissolution rate.

As discussed above, Bhardwaj selected a granule size large enough to coat, but small enough to not be ruptured during chewing. Such a consideration cannot be understood as being related to dissolution.

In the previous response to Office Action, Applicant provided select pages from *Remmington's Pharmaceutical Sciences* from both 1980 (top page 1563, column 1) and 1995 (bottom of page 898, column 2) Editions demonstrating that **one of skill in the art would understand granule size to be a manufacturing consideration**, with the granule size being selected based on the size of the tablet to be manufactured. Applicant again requests that a reference be provided to demonstrate that granule size, not API size, within the claimed range would be considered to be a **results effective variable for dissolution, not predominantly for manufacturing**.

Nemoto discusses in detail the effects of granule size on manufacturing. Further, reference is made to the teachings of Nemoto that variations of the formulations can alter the ability of granules to tablet properly (see page 3 of Nemoto). However, it is respectfully submitted that it would not be obvious that decreasing granule size could provide tablets with the appropriate hardness. The alleged teachings of desirable hardness of tablets by Ollinger provides no expectation that modification of the granule size would provide a tablet of the desired hardness. Simply wishing that granules of a particular size will produce a tablet of the desired hardness by pointing to a reference that tablets of specific hardnesses can be prepared does not provide a reasonable expectation of success.

It is well known that the presence of small granules, typically known as fines, result in tablets with inappropriate hardness. For example, as discussed on page 1563 Remmington's, 16th Edition (provided with the previous response) air trapped in the tablets by the fine powder causes them to split apart after ejection from the machine. Therefore, the final tablet hardness is partly a result of the granule size, with the

presence of excessive small particles providing inappropriate hardness of tablets. The appropriate hardness cannot be achieved using all particle sizes. There can be no expectation of success that by using the reduce granule size as instantly claimed that one could arrive at a tablet of the desired hardness.

The importance of the selection of an appropriate granule size and combination of components to allow for tableting is discussed by Nemoto. A goal of the granulation step of Nemoto was "**the production of granules having good fluidity**" (third full paragraph, page 3). Formation of granules is necessary for the formation of tablets and for filling capsules. Nemoto frequently comments about the inappropriateness of certain combinations of antacid and oxicams as they prevent the formulation of good granules and have undesirable properties that prevent tableting. Not only must the composition of Nemoto (and all of the other references cited) have good dissolution properties, it also must be appropriate for the formation of tablets or filling capsules. This is accomplished by Nemeto by using granulation. For example, Nemoto states:

> However, if more than 20 parts by weight are blended, hardness decreases thereby **preventing suitable tablets** from being obtained, and if more than 15 parts by weight are blended, the tablets are **subject to cracking and chipping** during coating. (last paragraph, page 2)
>
> If more than 40 parts by weight are blended, however, granulation becomes difficult, thereby **preventing the production of granules having good fluidity**… if more than 20 parts by weight are blended, the ease of forming of the granules becomes poor **causing the surface of the granules to chip during coating** (third paragraph, page 3) [emphasis added]

Therefore, an essential aspect of the Nemoto reference is the ability to form granules, and subsequently form tablets or fill capsules with them, **in addition** to being able to provide a composition with good dissolution properties.

Nemoto teaches against compositions that prevent good granulation. If proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984).

Nemeto repeatedly teaches that granulation is an essential aspect of the invention to prepare granules with "good fluidity" that can optionally be formed into tablets. Any modification that does not include the formation of granules with "good fluidity", e.g., by formation of granules taught by the art to have poor flow, i.e., granules smaller than about 200 µM, would render the reference unsatisfactory for its intended purpose and therefore be impermissible.

Lieberman, as discussed above, suggests that granules of the instantly claimed size would not necessarily have the desired flow properties. Applicant requests that the Examiner provide a reference **related to formulation of pharmaceutical compositions for tableting or filling of capsules** demonstrating that one of skill in the art would expect that of granules of the claimed size would result in a pharmaceutical composition appropriate for tableting. Applicant notes that in the 10 formulations taught by Nemoto, there is no teaching or suggestion to modify the method of making granules for the preparation of tablets or capsules. Nemoto demonstrates variations in the specific components of the compositions, but **the methods of making the tablets are the same throughout all of the examples in the reference**. Nemoto neither teaches nor suggests that varying the method for tablet preparation could alter dissolution properties, or how one might alter methods of tablet preparation to alter dissolution properties. Therefore, based on the teachings of Nemoto one would not be motivated to vary the methods for preparation of tablets.

MPEP 2143.01 (III) states:

> The mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art. *KSR International Co. v. Teleflex Inc.,* 550 U.S. ___, ___, 82 USPQ2d 1385, 1396 (2007)("If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability. For the same reason, if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill."). [emphasis in the original]

The claimed invention is not a "predictable variation" of the teachings of Nemoto. In fact, Melia teaches that "disintegration of a tablet or capsule is a relatively rapid process and it is controlled principally by the disintegrant within the dosage form." That is Melia teaches that granule size is unimportant in relation to dissolution. The claimed invention is a variation not expected to be an operable composition for the desired purpose. Therefore, it cannot be obvious.

The MPEP notes that the results of the modification of the reference needs to be obvious and **there must be some motivation to modify the cited art** to make an obviousness rejection. Specifically, MPEP 2143.01 (IV) states:

> A statement that modifications of the prior art to meet the claimed invention would have been "'well within the ordinary skill of the art at the time the claimed invention was made'" because the references relied upon teach that all aspects of the claimed invention were individually known in the art is not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine the teachings of the references. *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993). "'[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.'" *KSR*, 550 U.S. at ___, 82 USPQ2d at 1396 quoting *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006). [emphasis in original]

There can be no "rational underpinning" to modify the teachings of Nemoto **to provide a composition that would be expected to have poor fluidity** by decreasing the particle size based on any of the references cited, either alone or in combination with each other.

For at least the reasons set forth above, claim 68, the independent claim pending in the case, cannot be obvious in view of any combination of the cited references. Decreasing granule size would result in granules that were not appropriate for preparations of appropriate dosages or tablets. All of the cited references, other than Melia, teach the formation of unit dosages and/ or tablets. At least Nemoto and Bhardwaj teach that a minimum granule size, at least 10 times the largest size particle taught by Melia, is needed for preparation of the pharmaceutical compositions. **The**

dissolution properties of a pharmaceutical composition are of no importance if an appropriate dosage form cannot be manufactured. The references cannot be combined as asserted and the rejection must fall.

As the remaining claims pending in the instant application are all dependent upon non-obvious claim 68, they also cannot be obvious in view of the cited art and the rejections fail for the same reasons. Reconsideration and the withdrawal of the rejections is respectfully requested.

New claims 123-124 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over Nemoto et al. (JP 03-240729) in view of Bhardwaj et al. (US 5,578,316), Melia et al. (*Aliment. Pharmacol. Therap*. (1989) 3, 513-525) and Klioze et al. (US 2,887,439).

Newly added claims 125-126 are rejected under 35 U.S.C. 103(a) as the limitation of the use of granulate particles is allegedly rendered obvious by the teachings of Nemoto.

Applicant submits that the rejection of the newly added claims fails for the same reason as the rejections maintained in the instant Office Action. The references cannot be combined as asserted in the Office Action; therefore, the rejection must fall. Decreasing the granule size of the pharmaceutical compositions in the cited references would make the material unusable for its intended purpose. Therefore, the modification cannot be proper.

It is believed that there is no fee due with this response. However, if a fee is due with this paper or any other paper filed by this firm in relation to this application, Applicant hereby authorizes the Commissioner to charge Deposit Account No. 04-1105 citing Docket No. 55682CON(71432). Credit of any overpayment is respectfully requested.

In view of the above amendments and remarks, Applicant believes the pending application is in condition for allowance. However, if the Examiner believes that there are any outstanding issues in the case that could be addressed by a telephone interview, the Examiner is encouraged to call the Agent for Applicant listed below.

Dated: September 28, 2009

Respectfully submitted,

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